

## The use of The Danish Newborn Screening Register and Biobank in Routine and Research

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## Summary

- ❖ Newborn screening in DK year 2006
- ❖ Legislation for newborn DBSS register and biobank
- ❖ Public debate now and in the past
- ❖ Storage of DBSS specimens and data
- ❖ Practical use in routine and in research
- ❖ New Biobank Guidelines

## Routine newborn screening for PKU (1975), CH (1978), and Toxoplasmosis (1999) in Denmark, Greenland and Faroe Island

- ❖ Mandatory to offer screening
- ❖ Informed dissent (+/- screening, - storage)
- ❖ PKU-Biobank since 1982
- ❖ 30 mill Euro saved per year
- ❖ Cost benefit ratio 1:28
- ❖ Accreditation: Iso 17025 by Danak 1998 and onwards
- ❖ New guidelines for newborn screening 2006

## Patient information



Pamphlets and Homepage ([www.ssi.dk](http://www.ssi.dk))

## Patient information

### Det drejer sig om følgende sygdomme:

**Phenylketonuri (PKU)** er en stoffskiftesygdom, som ubehandlet medfører, at barnet bliver svært udviklingshæmmet, lærd og følelsesmæssigt psykisk. Opdagelse af sygdommen tidligt vil barnet udvikle sig normalt med standardbehandling. PKU ses hos ca. 1 ud af 12.000 nyfødte og kaldes også fællessygdom.

**Medfødt medulær stoffskifte** skyldes arvelig sygdom og forekommer hos ca. 1 ud af 3.400 nyfødte. Hvis sygdommen ikke opdaget og behandlet, kan sygdommen føre til, at barnet udvikler sig normalt med hormonbehandling i piller. Medfødt medulær stoffskifte ses hos ca. 1 ud af 3.400 nyfødte.

**Medfødt toxoplasmose** skyldes, at moderen er blevet smittet med toxoplasmose under graviditeten. Ubehandlet kan sygdommen medføre, at barnet får medulær stoffskifte og følelsesmæssigt psykisk. Hvis sygdommen opdaget og behandlet, vil barnet udvikle sig normalt med hormonbehandling i piller. Medfødt toxoplasmose ses hos ca. 1 ud af 3.000 nyfødte.

Under barnet af en af de tre sygdomme, får forældrene straks besked og barnet indskrives til yderligere undersøgelser og behandling på nærmeste børnspecialist.

### Hvordan tages blodprøven?

Prøven tages som en blodprøve fra barnets hæl, når barnet er mellem 5 og 7 dage gammelt og ikke senere end 10. levedag. Prøven foretages med barnets navn, fødselsdato, vægt og svangerskabslængde. Desuden noteres moderens navn og CPR-nummer. Prøven sendes til Statens Serum Institut, der analyserer prøven.

Blodprøven opbevares på Statens Serum Institut under et låbenummer. Øvrige oplysninger opbevares adskilt fra blodprøven.

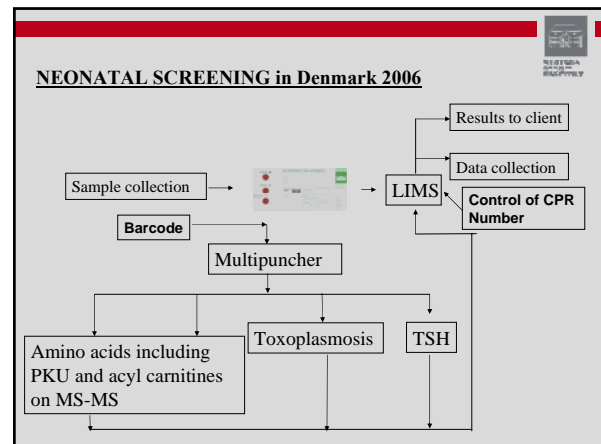
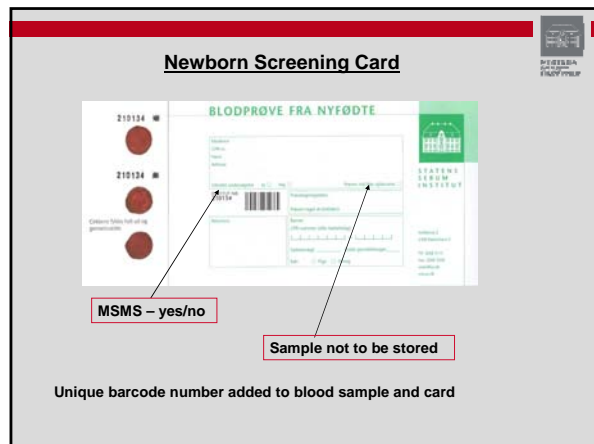
Det er vigtigt, at prøven opbevares for at:

- kunne gentage analysen eller udføre supplerende analyser, hvis barnet i sjældne tilfælde senere udvikler uhelbredelige arvelige sygdomme
  - kunne forebygge og udvikle nye analysemetoder
  - kunne anvende enkelte prøver til videnskabelig forskning, altid efter forudgående godkendelse af en videnskabetisk komité
- Oplys til dem, der tager blodprøven, hvis du ikke ønsker, at prøven opbevares.

## Screening of newborns (filter paper blood sample day 5-7)



Pamphlets and Homepage ([www.ssi.dk](http://www.ssi.dk))



### Public debate about the Danish PKU register 1991-1994

- News media – October 10, 1991
- The Danish Parliament
- The Danish National Board of Health
- The Council of Ethics
- The Central Scientific Ethical Committee
- On site – inspection September 17, 1993

### “Protection of sensitive personal information with special reference to genetic data”

- ❖ A Report by The Council of Ethics
- ❖ Public debate
- ❖ PKU register and Biobank - a Target

Danish Council of Ethics

### “Danish health information banks. Biobanks”

- ❖ A report by:
- ❖ The Danish Council of Ethics
- ❖ The Danish Medical Research Council
- ❖ The Central Scientific Ethical Committee

Danish Council of Ethics, Fax: +45 3537 5755

### Human biobanks - ethical and social issues

- ❖ A publication by the Nordic Committee on Bioethics edited by Marja Sorsa and Jörunn Eyfjörð
- ❖ Workshop: 2-5 1997 May in Reykjavik
- ❖ Participants: Ethicists, philosophers, theologians, physicians, scientists, lawyers, journalists, politicians and researchers from the pharmaceutical industry from the five Nordic Countries

Nordic Council, P.O. box 3043, DK-1021 Copenhagen, Fax: +45 3311 1870

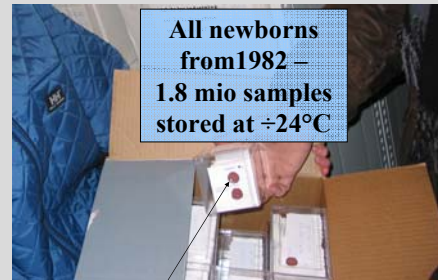
### Biobank use Info document to Ministry of Health

Describing procedures now and in the past concerning:

Diagnosis, treatment, control measures, documentation, repeated analyses, quality – assurance, assay improvements, non individual statistics, specific disease testing medico legal use and research projects. **No examples of misuse!**

Executive order/regulation by the Ministry of health (January 14th 1993)

### Danish neonatal DBSS Biobank



One 3 mm punch ~ approx. 3.2 µl blood

### The Danish Newborn Screening register and biobank

The stored information and biobank is used for:

1. Diagnosis and treatment of PKU, CH and Toxoplasmosis
2. Control, documentation and repeated analyses
3. Quality assurance and assay improvement
4. Non-individual based statistics
5. Specific disease testing (informed consent)
6. Medico legal use (court order)
7. Research projects using biochemical, genetical and environmental markers

### Specific disease testing using stored PKU cards (Ad 5)

- ❖ Pediatricians, Clinical Geneticists, Forensic Pathologists
- ❖ Informed consent
- ❖ Biochemical or mutational analyses
- ❖ Treatment ?
- ❖ Prevention ? (Prenatal Diagnosis)

### Diagnostic use during infancy

Unexpected morbidity/mortality

- ❖ Retrospective genetic testing ex. congenital epidermolysis bullosa CDG syndrome Long QT syndrome ex. Spinal muscle atrophy type 1 etc.
- ❖ Congenital infections Toxoplasmosis (IgM) CMV (IgM + PCR)

### Medico legal use (Ad 6)

- ❖ After informed consent or court order
- ❖ Infant death in early infancy
- ❖ Identification
- ❖ Crime scene investigations

### Research projects (Ad 7)

- ❖ Anonymous +/-
- ❖ Informed consent +/- or dissent
- ❖ Approval by the Data Surveillance Authority
- ❖ Approval by the Scientific Ethical Committee
- ❖ Final approval by Biobank Steering Committee

### Retrospective screening projects

Is prospective screening possible?

- ❖ Neonatal screening for CF (IRT +  $\Delta 508$ )
- ❖ Congenital Toxoplasmosis (IgM)
- ❖ Congenital adrenal Hyperplasia (17-OH-P)
- ❖ Tandem Mass Spectrometry (MS-MS)

### Allele frequency studies

- ❖ MCAD mutation and SIDS
- ❖ Apolipoprotein B-3500 m
- ❖ Factor V Leiden Mutation
- ❖ Hereditary haemochromatosis
- ❖ Luteinizing Hormone
- ❖ Follicle stimulating hormone receptor
- ❖ Transforming growth factor alpha and facial cleft
- ❖ Bylers disease
- ❖ Others

### Infectious disease epidemiology (mother & child samples)

- ❖ Toxoplasmosis
- ❖ Parvovirus B19
- ❖ HIV & Hep. B surveillance
- ❖ Vaccination status surveillance

### Case/control studies ("Late onset disorders") Etiology studies

- ❖ Cerebral palsy
- ❖ Diabetes Mellitus type 1
- ❖ Schizophrenia
- ❖ Bipolar disorders
- ❖ Autism
- ❖ Other

Type 1 diabetes risk analyses on dried blood spot samples from population based newborn.  
Design and feasibility of an unselected case control study

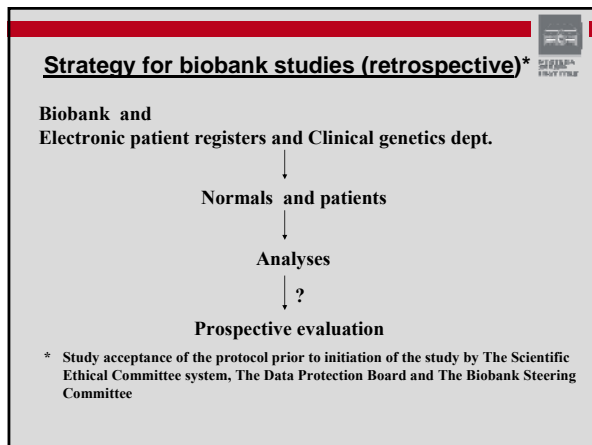
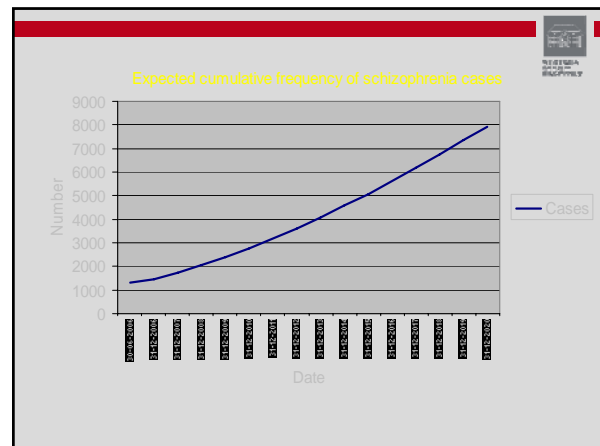
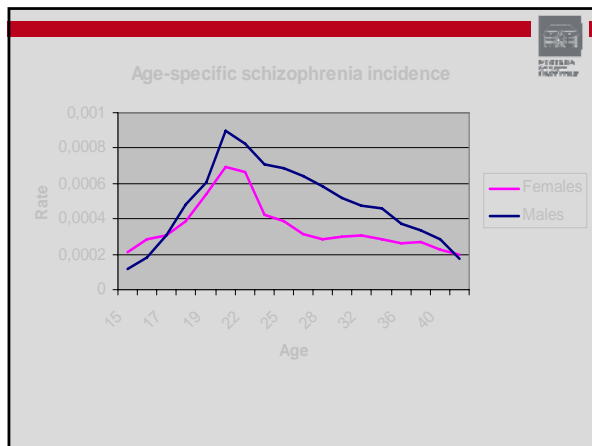
Eising S. et al: *Pediatric and Perinatal Epidemiology*. 2006; *In press*

#### Material:

T1D cases: 2086  
Controls: 4172

Analyses: genotyping  
cytokine measurements  
auto-antibody measurements

Information: Danish National registers



### The legal situation

- ❖ EU: Bioethics convention:
- ❖ §22 "appropriate consent" a must for new uses

### An account on Danish Biobanks (2002)

A task group:  
 Ministry of Interior & Health  
 Ministry of Science, Technology & innovation  
 Ministry of Justice

Objective: to protect the integrity of the donors and to give recommendations for new legislation

## Biobank definition

"A biobank is defined as a structural collection of human biological material which is accessible under certain criteria, and where information contained in the biological material can be traced back to individuals"

A biobank can be considered as "manual register" (non electronic register), which is subject to the Act on personal data processing (The Personal Data Act)

Interaction with other legislations such as:

Act on the Legal status of patients

Act on science-ethical committee system and treatment of biomedical research projects

Act on central management of the public health



## The legal situation

❖ **Denmark:** New legislation recently suggested (may 2002).

❖ Nationwide "Opt-out Registry" for subjects who do not a) wish any sample to be stored or b) do not wish that their samples are used for research

❖ Scientific, ethical committees will decide "whether or not" informed consent is necessary for new uses.

Meeting in Danish Parliament (Hearing)

2 October 2002



## Types of Biobanks according to new regulations

### Guidelines:

1. Clinical Biobanks used for health care purposes
2. Research Biobanks used for research only
3. Donor Biobanks used for treatment of a patient or a group of patients
4. Biobanks with other health care purposes e.g. stem cell Biobank, production Biobanks etc.



## Research and non-research projects (1)

- Ad 1 Clinical or health care Biobanks are collected and stored in relation to diagnosis and treatment, but may also be used for research
- Ad 2 Research Biobanks are collected and stored with research purpose only and informed consent, ex. The Danish National Birth Cohort



## Research and non-research project (2)

Pragmatic distinctions for newborn Biobank:

1. Close or distant from the original purpose
2. Internal/external involvement
3. Prospective/retrospective projects



## Use of newborn biobank material (DBSS)

1st priority:  
analytical purposes for the parents/child

2nd priority:  
development of new analytical methods for congenital diseases

3rd priority:  
research project



### A new biobank steering committee for research project

- An initiative from the Danish Medical Research Council
- Ensure that all guidelines are followed:
  - a) enough material left in biobank
  - b) accept from Scientific Ethical Committee System
  - c) accept from the Data Protection Board
  - d) extra material returned to biobank

### New filterpaper assays

Tandem mass spectroscopy (MSMS)  
(amino acids, organic acids and fatty acids)

New multiplex immunoassays  
(hormons, enzymes, cytokines, autoantibodies, etc.)

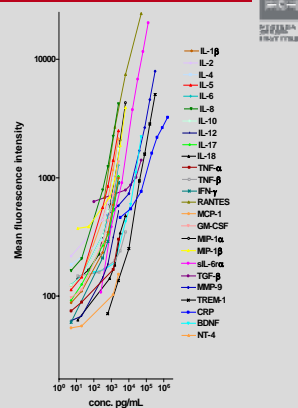
Whole genome amplification (WGA)  
(genetical analyzes)

Axelborg, 9. november 2005

Multianalyte assay for cytokines in PKU-blood spots

Mixtures of 25 recombinant standards spotted on filter paper. Extracts from two 3.2 mm punches are processed for triplicate determinations.

Skogstrand et al. 2005  
*Clin Chem*, 51: 1854-1866



### Danish newborn DBSS bank (1)

- ❖ Bank regulated by specific legislation with oversight
- ❖ Parents informed at specimen collection about bank and its use
  - Verbally and pamphlets
  - Information focuses on the use of specimens
- ❖ Parents may choose to opt out – now or later  
(central “Use of tissue register” for Denmark)

### Danish newborn DBSS bank (2)

#### Storage:

- ❖ Secured privacy protection/controlled access
- ❖ Linked with data/specimen in separate facilities
- ❖ Unique number assigned
- ❖ Computerized system
- ❖ Stored at -20°C without desiccant
- ❖ Freezer restricted to authorized personal only

### Danish newborn DBSS bank (3)

#### Legal and Ethical issues:

- ❖ Public debate – political, administrative and legal assessments
- ❖ Well-defined set of regulations for operations

Open dialogue important

### Conclusion (1)

Systematic storage of DBS residuals from newborn screening:

- ❖ A sine qua non for routine screening
- ❖ Beneficial to newborns, their families the society and future generations
- ❖ Strict rules and specific safety procedures
- ❖ Open and continuing evaluation and public dialog
- ❖ Adequate resources must be available



### Conclusion (2)

Informed consent forms with signature etc. will not be possible in Denmark

- ❖ Administration will be very complicated, expensive and time consuming
- ❖ Health professionals do not have time and motivation
- ❖ Will cause misunderstanding mistrust and anxiety
- ❖ Many will opt out from storage and screening

